AFFIDAVIT OF KUPPUSAMY NAGARAJAN

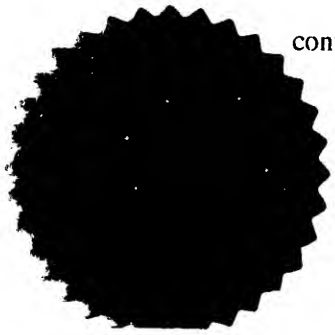
[IN THE MATTER OF U.S. Patent Application, Serial Number: 10/535,253]

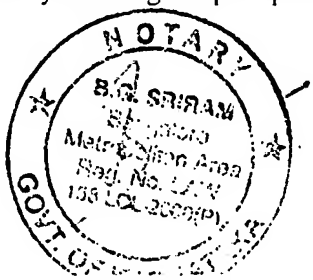
I, Kuppusamy Nagarajan citizen of India resident of (4A, Atishi Apartment,15th Main, Rose Garden Road, 5th Phase, J.P.Nagar, Bangalore – 560 078) do hereby solemnly and sincerely affirm and state as follows:

1. I am a co-inventor of the subject matter claimed in the U.S. Patent Application, Serial Number: 10/535,253.

2. I am currently (Corporate Advisor), at (Hikal Limited, 32/1, Kalena Agrahara, Bannerghatta Road, Bangalore – 560 076, Karnataka State, India). I have worked in the pharmaceutical field for more than 50years. I received a B.Sc (Hons) degree in (Chemistry) from Loyola College Madras in 1950, and a Ph.D Degree in 1954 from the Madras University. A copy of my curriculum vitae is attached.

3. The invention as claimed relates to an improved process for the preparation of gabapentin of formula I, which comprises (i) preparing an aqueous solution of Gabapentin hydrochloride in water in a ratio of one part by weight of the Gabapentin hydrochloride to 0.5 to 3 parts by weight of the water; (ii) preparing an aqueous solution of an alkali metal base in a concentration in the range of 40-50% w/w; (iii) adding 0.08 to 0.3 parts by weight of the solution obtained in step (ii) to 1.5 to 4 parts by weight of the solution obtained in step (i) at a temperature in the range of 0 to 20 degree C to form a resulting solution; (iv) heating the resulting solution gradually to a temperature in the range of 60-90 degree C; (v) gradually cooling the resulting solution to a temperature in the range of 0 to 15 degree C to obtain a precipitate; (vi) aging the precipitate for a period of time in the range of 0.5 hrs to 8 hrs at a temperature in the range of 0 to 15 degree C; (vii) separating the precipitate from its mother liquor by conventional methods; and (viii) recrystallising the precipitate from a mixture of





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isopropyl alcohol (IPA), methanol & water in a ratio ranging from 4.54-19.64 : 3.88-15.64 : 1 (v/v) to get Gabapentin of over 99.5% purity and another mother liquor, wherein the Gabapentin has a chloride content of 100 ppm or less.

4. The present process relates to the preparation of Gabapentin (chemically known as 1-aminomethyl-1-cyclohexaneacetic acid), which is a very well known agent useful for the treatment of epilepsy and other cerebral disorders. Gabapentin is a high selling drug and has been developed as having anti-convulsive properties. In addition, it can also be used for the treatment of deep neural pain.

5. One major aspect to be considered while developing a process for the preparation of gabapentin is regarding the purity of Gabapentin. The Pharmaceutical Forum has proposed the specifications regarding the purity of Gabapentin that is to be used in pharmaceutical applications/formulations. Some of these stipulations are as follows

1	Chloride content	Not more than 100ppm
2	Gabalactam content	less than 0.1%
3	Impurity with RF 0.5 relative to gabapentin	less than 0.2%
4	Any other individual impurity	less than 0.1%
5	Total impurities	less than 0.5% excluding the impurity mentioned in item 3

6. While developing the process for the preparation of Gabapentin, the inventors sought to develop a simple and economical process whereby it is possible to prepare Gabapentin having high purity (99.5%), in good yield of 40 to 60% and meeting all the stringent requirements for its use in the pharmaceutical field.

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7. Systematic investigations made were by the inventors with various volumes of water for dissolving gabapentin hydrochloride; with various strengths of neutralizing alkali; with various temperatures of neutralization; with various aging time of the precipitate; with various compositions of liquids for washing the filter cake; and with various crystallization procedures.

8. During the investigations, while seeking alternative crystallisation procedures with various solvent systems, the inventors unexpectedly found that by utilizing a combination of isopropyl alcohol, methanol and water as solvent system for recrystallisation, Gabapentin could be produced with high purity, meeting all the stringent requirements for its use in the pharmaceutical field.

9. The inventors also surprisingly found that Gabapentin was produced in higher yields when Gabapentin is recrystallised using isopropyl alcohol, methanol and water in a ratio ranging from 4.5-19.54: 3.88-15.84: 1 (v/v). The inventors also found that using a larger quantity of water reduces the yield of Gabapentin.

10. The inventors also found that the gabapentin produced from recrystallisation using isopropyl alcohol and methanol, without addition of water, has unacceptably high chloride content and thereby unsuitable for pharmaceutical applications.

11. Presented herein is data demonstrating these surprising and unexpected results. The following experiments were carried out under my direct supervision and control. The test results described herein establish the following facts:

A. Gabapentin prepared by recrystallisation from methanol isopropyl alcohol and water meets the pharmacopial limits.

B. Gabapentin prepared by recrystallization Methanol and Isopropyl alcohol only (each containing 0.1% moisture) has a chloride content that exceeds pharmacopial limit significantly.

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C. Using larger amount of water for recrystallisation results in significant fall in the yield of the final product.

12. Four experiments were conducted wherein different procedures were adopted for recrystallisation of Gabapentin. For these experiments, crude Gabapentin was obtained from neutralization of Gabapentin Hydrochloride in accordance with the procedure described in Example 1 of US2006/0149099 (the present application). The crude Gabapentin had a moisture content of 18% and about 1.0% of ash content as well as 1.0% of gabalactam. The crude Gabapentin was converted into anhydrous gabapentin in four different experiments. Methanol and Isopropyl Alcohol used in all of the following experiments contained about 0.1% moisture.

Recrystallisation of Gabapentin from Methanol Water and Isopropyl alcohol produces a product meeting all pharmacopial requirements

13. The first experiment was conducted wherein Gabapentin was recrystallised using isopropyl alcohol, methanol and water following the procedure as disclosed in Example 1 of US2006/0149099 (the present) application. The crude gabapentin (25g, equivalent to 32.5 of gabapentin hydrochloride hemihydrate, moisture content 18% and ash content about 1.0%) was dissolved in a mixture of methanol (73.1ml) and water (7.69ml) at about 70°C. The solution was treated with activated charcoal (0.16g) and filtered through a bed of hyflo. The bed was washed with a mixture of methanol (5.96ml) and water (0.27ml). To the combined filtrates was added isopropyl alcohol (99.63ml). The mixture was cooled to 0-5°C and maintained for 1.0 hour, when pure white gabapentin crystallized out; the mixture was centrifuged; the product was spin dried for 45 minutes and dried to yield gabapentin (14.9g, yield 58%).

1. Chloride content - 90ppm
2. Gabalactam – 0.007%
3. Polar impurity (RRt 0.5) – 0.02%

4. Any other impurity less than 0.1%

5. Total impurities - 0.07%.

Recrystallisation of Gabapentin from Isopropyl alcohol, Methanol and Water using excess water results in a significant fall in the yield of the final product.

14. An experiment was conducted to assess the effect of increasing the amount of water used for recrystallisation of the final product. Crude Gabapentin (25g, equivalent to 32.5 of gabapentin hydrochloride hemihydrate, moisture content 18% and ash content about 1.0%) was dissolved in a mixture of methanol (73.1ml) and water (46.48ml) at about 70°C. The solution was treated with activated charcoal (0.16g) and filtered through a bed of hyflo. The bed was washed with a mixture of methanol (5.96ml) and water (0.27ml). To the combined filtrate was added isopropyl alcohol (99.63ml). The mixture was cooled to 0-5°C and maintained for 1.0 hour, when pure white gabapentin crystallized out; the mixture was centrifuged; the product was spin dried for 45minutes and dried to yield gabapentin (6.0g, yield 23.4%).

1. Chloride content - 25 ppm
2. Gabalactam – 0.004%
3. Polar impurity (RRt 0.5) - ND
4. Any other impurity less than 0.1%
5. Total impurities - 0.03%

Recrystallisation of Gabapentin from Methanol and Isopropyl alcohol only produced Gabapentin with significantly high chloride content.

15. Experiment was conducted wherein gabapentin was recrystallised using Isopropyl alcohol and Methanol, without addition of water. The crude gabapentin (25g, equivalent to 32.5 of gabapentin hydrochloride hemihydrate, moisture content 18% and ash content about 1.0%) and methanol (73.1ml) were heated to about 70°C. The suspension was treated with activated charcoal

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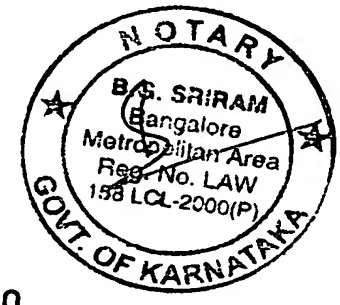
(0.16g) and filtered through a bed of hyflo. The bed was washed with methanol (5.9ml). To the combined filtrates was added isopropyl alcohol (99.63ml). The mixture was cooled to 0-5°C and maintained for 1.0 hour, when pure white gabapentin crystallized out; the mixture was centrifuged; the product was spin dried for 45 minutes and dried to yield gabapentin (11.5g, yield 44.8%).

1. Chloride content - 1200ppm
2. Gabalactam - 0.006%
3. Polar impurity (RRt 0.5) - 0.026%
4. Any other impurity less than 0.1%
5. Total impurities - 0.096%

Recrystallisation without water but adding more methanol to complete dissolution and more isopropyl alcohol to complete precipitation produced Gabapentin with significantly high chloride content.

16. Another experiment was conducted for recrystallisation of gabapentin from methanol and isopropyl alcohol, without addition of water, wherein a larger amount of methanol was used as compared to the experiment as in paragraph 16 above. The gabapentin (25g, equivalent to 32.5 of gabapentin hydrochloride hemihydrate, moisture content 18% and ash content about 1.0%) was dissolved in methanol (143ml) at about 70°C. The solution was treated with activated charcoal (0.16g) and filtered through a bed of hyflo. The bed was washed with methanol (6.0ml). To the combined filtrates was added isopropyl alcohol (179.68ml). The mixture was cooled to 0-5°C and maintained for 1.0hour, when pure white gabapentin crystallized out; the mixture was centrifuged; the product was spin dried for 45minutes and dried to yield gabapentin (16.2g, yield 63%)

1. Chloride content - 1000ppm
2. Gabalactam - 0.002%.
3. Polar impurity (RRt 0.5) - 0.025%



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4. Any other impurity less than 0.1%

5. Total impurities - 0.084%.

17. The inventors thus surprisingly found that recrystallization of crude Gabapentin using isopropyl alcohol, methanol and water, in a solvent ratio ranging from 4.5-19.54: 3.88-15.84: 1 (v/v) results of Gabapentin with high purity, in good yield and meets all the stringent pharmacopial requirements.

18. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true.

Date: 18/03/2009 By: Dr.K.Nagarajan

To be notarized

Sworn to. Signed before me

NOTARY REGISTER
SL. No. 1450-2009.
Dt. 18 MAR 2009

B. G. SRIRAM
ADVOCATE & NOTARY
Metropolitan Area Bangalore City
No. 82, 10th 'C' Main Road, 1st Block.
Jayanagar, BANGALORE - 560 011

NOTARY
B.G. SRIRAM
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My Term Expires on
12-5-2012

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BIOGRAPHICAL DATA

Name	:	Dr.K.Nagarajan
Date of Birth	:	September 15, 1930
Place of Birth	:	Sirupalai Village, Villupuram Taluka, Tamil Nadu
Father's Name	:	K.Kuppuswamy Iyer
Mother's Name	:	K.Rajammal
Family Status	:	Wife, Padmalochana Nagarajan, accomplished Bharatha Natyam Dancer and professional Carnatic Vocalist Daughter, Shobhana, accomplished Bharatha Natyam artiste, married and living in U.S.A Son, Srivatsan, Ph.D in Chemistry from University of Chicago, postdoctor at Caltech, Pasadena, Currently working for Avery Dennison, Pasadena, USA
High School Education	:	P.S.High School, Madras 4 (1939-1941) Ramakrishna Mission Residential School, Uttiramerur, Madras (1943-1945)
College Education	:	Presidency College Madras 5. Inter (1945-1947) Loyola College, Madras B.S.c.(Hons.) in Chemistry (1947-1950) Diploma in German (1956) Certificate in French (1957) (both of Madras University)

Academic

Distinctions etc	:	First Class throughout: several merit scholarships
Research Training	:	Under Prof.T.R.Govindachari Presidency College Ph.D of Madras University in 'Studies on Aporphine Alkaloids' (1954)

Post-doctoral Experience:

a. C.S.I.R Assistant in Presidency college on Chemical Investigations of Indian Medicinal Plants, 1954-1957.

b. Post-doctoral Fellow with Prof.C.L Stevens, Wayne State University, Detroit, U.S.A., 1957-1559.

c. Post - doctoral Fellow .with Prof. J.D. Roberts, California Institute of Technology, Pasadena, California, U.S.A , 1959-1960

d. Post-doctoral Fellow , Presidency College, Madras 5, 1960-1961

e. Post-doctoral Fellow with Prof.H.Schmid, Zurich University, Zurich, Switzerland, 1961-1962.

f. Trainee at CIBA AG., Basle Switzerland, 1962.

g. Exchange Scientist at CIBA Pharmaceutical Co., New Jersey, 1967.

Positions held and Responsibilities:

Head of Department of Medicinal Chemist:y and Manager, Hindustan CIBA-Geigy LTD., Research Centre, Bombay - 400 063

From January 1963 till June 1984, was in-charge of Synthetic Medicinal Chemistry carried out by a group of 5 senior scientists and 10 scientific assistants and later, Head of the Chemistry Group (scientific staff 25); coordinating with biology, toxicology, drug metabolism, clinical investigation; etc well-versed in Research

Management; represented the Research Centre in intramural International Research Conferences.

Director, R&D Centre, Searle (India) Limited., Bombay 1984-1992 (involved in the establishment of the Centre)
Director, Recon R&D Centre, Bangalore - 560 083, April 1992 - March 2000(established the center)
Advisor, Rallis R&D Centre, Bangalore - 560 076, Arpil 2000 - March 2001
Advisor, Hikal R&D centre, Bangalore - 560 076, March 2001 -

Areas of interest and professional experience

1. Synthetic heterocyclic chemistry directed towards new drugs - over 17000 compounds prepared, about 14,000 being synthetic entities, the rest plant products, for biological evaluation; more than 2000 synthesised personally; about 20 new chemical entities were taken up for clinical trials for diverse indications ranging from filaria to hypertension; antidepressant Sintamil being sold and marketing permissions obtained for ftranquillizer, Taomax, nasal decongestant, Varsyl' anthelmintic, ancletol and antiprotozal, Satranidazole(marketed by Alkem laboratories in March 2000). A promising and novel anti TB preparation,CGI 17341 was extensively investigated. Specially interested in antifertility, antiprotozoal, anthelmintic, antiinfective and antidiabetic drugs. A luminal amoebicide is under clinical trial in India and is also exported. The immunosuppressant, azathioprine has been made available through indigenous process development and has won a Vasvik award for the co-worker.

Drug design and molecular modeling

ii. Development of processes for a large number of other drugs like anti-bacterials.
iii. Custom chemical synthesis; contract research
iv. Natural products including alkaloids, terpenes, oxygen heterocycles, antibiotics, nucleosides, peptides, carbohydrates; especially interested in developing Ayurvedic products.
v. Small ring compounds.
vi. Discovery of several novel reactions and elucidation of their mechanisms a new method of peptide synthesis.
vii. Studies in nuclear magnetic resonance spectroscopy - 1H, 13C, 15N, 31P
viii. Process development and formulations of pesticides, like cypermethrin, flucythrinate, MTI 500, Butachlor, MON 7400

Publications:

About 280 in national and international journals.

Patents:

Filed patent applications in India and abroad for compounds with cardiovascular, antidepresssant, anticonvulsant, antifertility, anthelmintic, antiparasitic and antidiabetic activities; patents are filed also in India for the drug, quinfamide and for several pesticides like diflubenzuron and MTI 500.

Professional recognitions, honours etc:

Shanti Swarup Bhatnagar Prize for Chemical Sciences for 1974.

Lifetime Achievement Award, 2004 from Chemical Research Society of India.

Fellow of Indian National Science Academy (FNA), Indian Academy of Sciences (F.A.Sc.), Maharashtra Academy of Sciences, New York Academy of Sciences.

Invited to give lectures at several Indian as well as foreign universities, Wayne State University, Detroit; University of California, Irwine, California; Arizona State University, Tempe, Arizona; Zurich University, Berne University, Switzerland; University of Wurzburg, Koln University, University of Marburg, Germany; University of Paris, Centre for Research in Natural Products, Gif-sur-Yvette, France. Industrial laboratories; Endo Laboratories, New York, CIBA Pharmaceutical Co., New Jeresy and CIBA AG, Basle.

Participated in national workshops and international symposia - invited to be co - chairman for one of the sessions of IUPAC Natural Products Symposium held in Delhi in February 1972, and for 10th International Conference on Organic Synthesis, Bangalore, December 1994.

Referee for Ph.D thesis of several Indian universities; Member of Selection, Promotion, Assesment Committees of CSIR laboratories: former member, Executive Committee, PID, RAC - NCL of CSIR; and RC member of IICT.Currently R.C. member of RRL, Jammu. Referee of CSIR, UGC, DST Schemes, with good contacts of concerned officials; member, Faculty of Science, Cochin University; former member of PAC, DST; member of CSIR committee for Organic Chemistry.

Visiting Lecturership under INSA-Royal Society, England Exchange Programme for 1982-83; INSA - French Academy of Sciences for 1984-85; Polish Academy of Sciences, 1988-89-Seminars in several institutions during these visits.

Past President, Indian Chemical Society, Bombay branch. Former member, Editorial Board, Indian Journal of Chemistry, 1976-79, Proceedings of the Indian National Science Academy, 1978 -80, Proceedings of the Indian Academy of Sciences , Indian Journal of

Pharmacy; Aromatic and Medicinal Plants of India; Chairman, Board of Trustees of National Organic Symposium Trust.

Chevalier Machado Endowment Lectures at Madurai University; also lectures under the visiting Professorship Scheme, January, 1979.

Prof.K.Venkataraman Endowment Lecture, Bombay University, February 1979; Dr.Shah Endowment LectureBombay University, 1989; Dr.Suresh Sethna Endowment Lecture, M.S.University, Baroda, 1988; Plantinum Jubilee Lecture of Indian Science Congress, March 1995.

Member of several professional societies

Extracurricular Activities:

Interested in games like tennis, table-tennis, badminton, carrom.

Interested in classical Carnatic and Hindustani music and dance; helped in publication of a treatise 'Spiritual Heritage of Thyagaraja'

Interested in gardening, especially in roses.

Miscellaneous:

Marquis who is who in the world - 14th Edition

Addresses to which communications can be sent:

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